Cystic Fibrosis, Oral
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
ivacaftor (Kalydeco®)[1]	Vertex	Treatment of cystic fibrosis (CF) in patients age 2 years and older who have one of the following mutations in the *CFTR* gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *R117H, S1251N*, *S1255P*, *S549N*, or *S549R* Limitation of use: not effective in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene*
lumacaftor/ivacaftor (Orkambi®)[2]	Vertex	Treatment of CF in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene Limitation of use: safety and efficacy have not been established in patients with CF other than those homozygous for the *F508del* mutation

* A 16-week clinical trial assessing the efficacy of ivacaftor for the treatment of patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene found no improvement in forced expiratory volume in 1 second (FEV_1) compared to placebo.[3]

OVERVIEW

Cystic Fibrosis (CF) is a serious autosomal recessive multiorgan disorder. Mutations lead to disease of the exocrine gland function, resulting in the formation of thick mucus that builds up in the lungs, digestive tract, and other parts of the body.[4] CF, which affects about 30,000 people in the United States (U.S.), is the most common fatal genetic disease in Caucasians.[5,6] Heterozygote frequency is approximately 1 in 20. In the U.S., prevalence is highest in Caucasians (1 case per 3,200 to 3,500 people) and lowest in Asian Americans (1 case per 31,000 people).[7] The median survival in patients with CF is 36.9 years with 80% of patients reaching adulthood. Children are anticipated to live to approximately 40 years of age with current treatments. In 2014, adults comprised approximately 50.7% of the CF population while in 1986, they comprised approximately 29.2%. Females with CF tend to have a more rapid deterioration and earlier death compared to males with CF.

In CF, a defect in the gene coding for the CF transmembrane conductance regulator (*CFTR*), which functions as chloride channel regulated by cyclic adenosine monophosphate (cAMP), results in abnormalities of chloride transport across epithelial cells on mucosal surfaces.[8] Decreased chloride secretion increases reabsorption of sodium and water, decreasing the hydration of mucus and promoting infection and inflammation. CF leads to severe respiratory and digestive problems, as well as other complications such as infections and diabetes. Pulmonary disease occurs in approximately 90% of those who survive the neonatal period, and end-stage lung disease is the primary cause of death. Pancreatic insufficiency decreasing intestinal absorption and intestinal obstruction are among other concerns in patients with CF. Diagnosis of CF is based on pulmonary and gastrointestinal manifestations, family history, and a positive sweat chloride test; however, newborn screening is universally offered in the U.S.

To date, over 1900 *CFTR* mutations have been identified.[9] Various classes of defects have been described: (class I) defective *CFTR* production, (class II) defective protein processing, (class III) disordered regulation (reduced ATP binding and hydrolysis), (class IV) defective chloride conductance or channel gating, (class V) reduced amounts of functioning CFTR/diminished transcription, and (class VI) increased turnover/shortened time at plasma membrane).[10,11] The F*508del (a class II mutation and*

also known as Phe508del) mutation is the most common cause of CF, occurring in approximately 45% of CF patients in the U.S. have two copies (one inherited from each parent) of the F*508del* mutation, which nearly always confers as pancreatic component.[12,13] However, genotype does not consistently correlate with phenotype. Certain mutations are associated with certain groups, such as the W1282X allele in those of Ashkenazi Jewish descent. The most common class III mutation is G551D (4% of those with CF worldwide).[14] Other common mutations affecting *CFTR* gating include *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *G970R*, and *S549R*. The *R117H* mutation, a class IV mutation, leads to a faulty ion channel.[15]

Goals of CF treatment include maintaining lung function by controlling infection and clearing mucus in the airway, maintaining appropriate growth by providing nutritional support (e.g., enzyme, mineral, and multivitamin supplements, and managing disease complications (e.g., insulin therapy in patients who develop diabetes).[16] Treatment of CF is mainly dependent on the type and severity of CF symptoms, and this can differ widely from person to person.[17] Medication therapy for respiratory complications primarily includes antibiotics (oral, intravenous [IV], inhaled) as well as other treatments (e.g., bronchodilators, anti-inflammatory agents, and mucolytics such as dornase alfa [Pulmozyme®]) for airway clearance. *CFTR* potentiators are the newest class of medications available for this disease and improve chloride ion transport abnormalities. The U.S. Food and Drug Administration (FDA) approved ivacaftor (Kalydeco) in 2012 and lumacaftor/ivacaftor (Orkambi) in 2015.[18,19] Each agent is approved for differing *CFTR* genotypes. If a patient's genotype is unknown, an FDA-approved CF mutation test should be used to detect the presence of a *CFTR* mutation. This should be followed by verification if needed based on recommendations of the mutation test. Use of these agents does not eliminate the need for other symptomatic and preventative therapy; rather, their treatment is intended to improve the functionality of the *CFTR* protein.

The Cystic Fibrosis Foundation (CFF), which tracks and reports CF data and provides resources to patients, caregivers, and medical providers, published updated guidelines on chronic medications for the maintenance of lung health in CF patients in 2013.[20] The CFF continues to recommend inhaled treatments (e.g., tobramycin, dornase alfa, hypertonic saline, corticosteroids) and oral treatments (e.g., antibiotics, corticosteroids) for treatment of symptoms, exacerbations, and/or infections in patients with CF. With the update, CFF added the recommendation of chronic treatment with ivacaftor for individuals 6 years of age and older with at least one *G551D CFTR* mutation to improve lung function and quality of life and to reduce exacerbations (Recommendation: A). Ivacaftor had not received approval in younger patients (≥ 2 years of age) or the additional mutations at the time of publication. Likewise, lumacaftor/ivacaftor was not approved in 2013. The CFF has also published guidelines on newborn screening, diagnosis, nutritional, GI related issues, other respiratory care, and infection control.[21]

The Clinical Pharmacogenetics Implementation Consortium (CPIC) 2014 guidelines for ivacaftor therapy based on *CFTR* genotype recommend ivacaftor in CF patients ≥ 6 years old who are homozygous or heterozygous for the *G551D CFTR* variant.[22] CPIC further states that there are no data regarding whether or not ivacaftor can replace other established therapy. Like the CFF guidelines, CPIC developed these guidelines prior to the approval of lumacaftor/ivacaftor and the expanded indication approvals (other mutations, younger age) of ivacaftor.

This therapeutic class review focuses on the oral agents FDA-approved for the treatment of CF and includes ivacaftor (Kalydeco) and lumacaftor/ivacaftor (Orkambi).

PHARMACOLOGY[23,24]

Ivacaftor (Kalydeco, Orkambi) is a potentiator of the *CFTR* protein, a chloride channel on the surface of epithelial cells in multiple organs. This potentiation of the channel-open probability of the *CFTR* protein facilitates increased chloride ion transport.

The F508del mutation on the *CFTR* protein results in protein misfolding, leading to a less stable protein. Lumacaftor, the remaining component of Orkambi, improves the conformational stability of the F508del-*CFTR* protein. This increases the processing and trafficking of the mature protein to the cell surface, ultimately increasing chloride ion transport.

PHARMACOKINETICS[25,26]

Drug	Absorption (T_{max})	Metabolism	Elimination
ivacaftor	4 hours	Extensively metabolized by CYP3A to major metabolites: M1 (active), M6 (inactive)	Route: feces (87.8%), renal (negligible) $T_{1/2}$: 12 hours (9.34 hours with lumacaftor)
lumacaftor	4 hours	Limited metabolism by oxidation and glucuronidation	Route: feces (51%), renal (8.6%) $T_{1/2}$: 25.2 hours

T_{max} = time to maximum serum concentration, $T_{1/2}$ = half-life, V_d = volume of distribution

*Lumacaftor data reported (ivacaftor data is the same as reported with the individual product unless noted due to the induction effect of lumacaftor on ivacaftor).

The exposure of lumacaftor (Orkambi) in healthy adults is approximately twice as high as exposure in CF patients, while the exposure of ivacaftor (Kalydeco, Orkambi) is similar between healthy and CF patients.

The absorption of ivacaftor (Kalydeco) was increased by approximately 2.5- to 4-fold when administered with fatty food. The absorption of lumacaftor and ivacaftor (Orkambi) were increased by approximately 2-fold and 3-fold when administered with fatty food, respectively. Both ivacaftor and lumacaftor/ivacaftor should be administered with fat-containing food.

CONTRAINDICATIONS/WARNINGS[27,28]

Contraindications

Ivacaftor (Kalydeco) and lumacaftor/ivacaftor (Orkambi) lack specific contraindications.

Warnings

Elevated transaminases (alanine aminotransferase [ALT] or aspartase aminotransferase [AST]) have been reported with ivacaftor (Kalydeco) use. AST and ALT should be assessed at baseline, every 3 months during the first year of therapy, and annually thereafter, although more frequent monitoring may be appropriate in patients with a history of transaminase elevations. Close monitoring is needed until elevations resolve, but dosing should be interrupted if elevations of ALT or AST > 5 times the upper limit of normal (ULN) occur.

Elevated transaminases (ALT or AST) also have been reported with lumacaftor/ivacaftor (Orkambi) use, and some instances have been associated with concomitant total serum bilirubin elevations. AST, ALT, and bilirubin should be assessed at baseline, every 3 months during the first year of therapy, and

annually thereafter, although more frequent monitoring may be appropriate in patients with a history of transaminase or bilirubin elevations. Close monitoring is needed until elevations resolve, but dosing should be interrupted if elevations of ALT or AST > 5 times ULN without an elevation in bilirubin or ALT or AST > 3 times ULN with an elevation in bilirubin (> 2 times ULN) occur.

Worsening liver function, including hepatic encephalopathy, has been reported in patients with advanced liver disease who were receiving lumacaftor/ivacaftor. Use cautiously and monitor closely if used in this population; a dose reduction is required.

Respiratory events, such as chest discomfort, abnormal respiration, or dyspnea, occurred more commonly in clinical trials during initiation with lumacaftor/ivacaftor than with placebo. Data in patients with a percent predicted forced expiratory volume in one second ($ppFEV_1$) < 40 is limited; additional monitoring is recommended during initiation of lumacaftor/ivacaftor.

Cases of non-congenital lens opacities/cataracts have occurred in pediatric patients using ivacaftor and lumacaftor/ivacaftor; baseline and follow-up ophthalmological examinations are recommended in pediatric patients starting treatment.

Efficacy of ivacaftor (Kalydeco, Orkambi) may be decreased by cytochrome P450 3A (CYP3A) inducers (e.g., rifampin, St. John's wort); coadministration is not recommended. Lumacaftor, a component of Orkambi, is a strong inducer of CYP3A, and may limit efficacy of medications that are sensitive substrates of CYP3A or are CYP3A substrates with a narrow therapeutic index when they are coadministered. Lumacaftor/ivacaftor may also decrease hormonal contraceptive exposure; hormonal contraceptives should not be relied on as an effective method of contraception. Drug interactions are detailed below.

DRUG INTERACTIONS[29,30]

Ivacaftor (Kalydeco) is a substrate of CYP3A. Concomitant use with a strong CYP3A inhibitor (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin) may increase exposure of ivacaftor; the following dose reduction is recommended in this population: one 150 mg tablet twice weekly in patients ≥ 6 years old, one 50 mg packet of oral granules twice weekly in patients 2 to < 6 years old with a body weight of < 14 kg, and one 75 mg packet of oral granules twice weekly in patients 2 to < 6 years old with a body weight of ≥ 14 kg.

Concomitant use with a moderate CYP3A inhibitor (e.g., fluconazole, erythromycin) may increase exposure of ivacaftor (Kalydeco); the following dose reduction is recommended in this population: one 150 mg tablet once daily in patients ≥ 6 years old, one 50 mg packet of oral granules once daily in patients 2 to < 6 years old with a body weight of < 14 kg, and one 75 mg packet of oral granules once daily in patients 2 to < 6 years old with a body weight of ≥ 14 kg. Likewise, coadministration with grapefruit juice or Seville oranges, moderate CYP3A inhibitors, should be avoided.

Strong CYP3A inhibitors are not expected to affect net exposure of ivacaftor when used in combination with lumacaftor (as Orkambi) due to the induction effect of lumacaftor. No dosage adjustment is needed when CYP3A inhibitors are initiated in patients already taking lumacaftor/ivacaftor, but a reduction of lumacaftor/ivacaftor to 1 tablet once daily for the first week followed by normal dosing is recommended when it is first initiated in a patient already receiving a CYP3A inhibitor.

Strong CYP3A inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort) may decrease the efficacy of ivacaftor and lumacaftor/ivacaftor; coadministration is not recommended.

Ivacaftor and its metabolite may inhibit CYP3A and P-glycoprotein (P-gp) while lumacaftor is a CYP3A inducer; coadministration with sensitive substrates of these enzymes (e.g., digoxin, cyclosporine, tacrolimus, midazolam, triazolam) may affect their exposure, potentially altering their therapeutic effect or leading to adverse events or inefficacy. Caution and careful monitoring is recommended when one of these agents is used concomitantly with ivacaftor.

Lumacaftor has the potential to induce CYP2B6, CYP2C8, CYP2C9, CYP2C19, and inhibit CYP2C8 and CYP2C9, and inhibit and induce P-gp. The use of lumacaftor/ivacaftor with substrates of these pathways (e.g., warfarin, digoxin) should be carefully monitored.

Lumacaftor/ivacaftor may decrease the exposure of prednisone, methylprednisolone, ibuprofen, certain antidepressants (e.g., citalopram, escitalopram, sertraline), repaglinide, sulfonylureas, proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole) and ranitidine. A higher dose of these medications may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor also may decrease exposure of montelukast, but no dose adjustment is recommended.

Concomitant use of lumacaftor/ivacaftor may decrease the exposure of certain antibiotics (e.g., clarithromycin, erythromycin, and telithromycin) and antifungals (e.g., itraconazole, ketoconazole, posaconazole, and voriconazole), which may reduce their effectiveness; an alternative should be considered.

Lumacaftor/ivacaftor may decrease hormonal contraceptive exposure, reducing effectiveness. Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with lumacaftor/ivacaftor.

Concomitant use of lumacaftor/ivacaftor with hormonal contraceptives increased menstrual abnormality events. Avoid concomitant use unless the benefit outweighs the risks.

ADVERSE EFFECTS[31,32]

Drug	Diarrhea	Nausea	Nasopharyngitis	Rash	URTI
ivacaftor (Kalydeco)	13 (7)	12 (11)	15 (12)	13 (7)	22 (14)
lumacaftor/ ivacaftor (Orkambi)	12 (8)	13 (8)	13 (11)	7 (2)	10 (5)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Serious adverse reactions occurring more frequently with ivacaftor than placebo were abdominal pain, increased hepatic enzymes, and hypoglycemia (frequency not reported).

Serious adverse reactions that occurred in ≤ 1% of patients taking lumacaftor/ivacaftor but more frequently than placebo included pneumonia, hemoptysis, cough, increased blood CPK, and transaminase elevation. Menstrual abnormalities also occurred more frequently with lumacaftor/ivacaftor (10%) than with placebo (2%) and were more common in those using hormonal contraceptives than those not using hormonal contraceptives.

SPECIAL POPULATIONS[33,34]

Pediatrics

The safety and efficacy of ivacaftor (Kalydeco) have not been established in patients with CF < 2 years old.

The safety and efficacy of lumacaftor/ivacaftor (Orkambi) in patients with CF < 12 years have not been established.

Pregnancy

Ivacaftor (Kalydeco) and lumacaftor/ivacaftor (Orkambi) are Pregnancy Category B and should be used during pregnancy only when clearly needed. There are no adequate and well-controlled trials of lumacaftor-ivacaftor or its individual components, lumacaftor or ivacaftor, in pregnant women.

Hepatic Impairment

No dosage adjustment of ivacaftor (Kalydeco) is required in patients with mild hepatic impairment (Child-Pugh Class A). A reduced dose of ivacaftor once daily is recommended in patients with moderate hepatic impairment (Child-Pugh Class B): one 150 mg tablet once daily in patients ≥ 6 years old, one 50 mg packet of oral granules once daily in patients 2 to < 6 years old with a body weight of < 14 kg, and one 75 mg packet of oral granules once daily in patients 2 to < 6 years old with a body weight of ≥ 14 kg. There is no data in patients with severe hepatic impairment (Child-Pugh Class C), but exposure is expected to be higher than seen in patients with moderate hepatic impairment. In this population, 1 tablet or 1 packet of granules may be used once daily or less frequently with caution.

No dosage adjustment of lumacaftor/ivacaftor (Orkambi) is required in patients with mild hepatic impairment (Child-Pugh Class A). A reduced dose of lumacaftor/ivacaftor of 2 tablets in the morning and 1 tablet in the evening is recommended in patients with moderate hepatic impairment (Child-Pugh Class B). There is no data in patients with severe hepatic impairment (Child-Pugh Class C), but exposure is expected to be higher than seen in patients with moderate hepatic impairment. In this population, 1 tablet in the morning and 1 tablet in the evening, or less, is recommended with caution.

Renal Impairment

Ivacaftor (Kalydeco) and lumacaftor/ivacaftor (Orkambi) have not been studied in patients with any degree of renal impairment (e.g., mild, moderate, severe, or end-stage renal disease [ESRD]); however, no dosage adjustment is recommended with either product in patients with mild or moderate renal impairment. Caution is recommended in patients with severe renal impairment (estimated creatinine clearance [CrCl] < 30 mL/min) or ESRD.

Patients with Severe Lung Dysfunction

Phase 3 trials of lumacaftor/ivacaftor (Orkambi) included 29 patients with $ppFEV_1 < 40$ at baseline. The treatment effect in this subgroup was comparable to that observed in patients with $ppFEV_1 \geq 40$.

DOSAGES[35,36]

Drug	Dosing*	Available Strengths
ivacaftor (Kalydeco)	Adults and children ≥ 6 years of age: one 150 mg tablet orally every 12 hours (300 mg/day); Children 2 to < 6 years old and ≥ 14 kg: one 75 mg packet (oral granules) every 12 hours (150 mg/day); Children 2 to < 6 years old and < 14 kg: one 50 mg packet (oral granules) every 12 hours (100 mg/day); All doses should be administered with fat-containing food Oral granules should be mixed with 5 mL of age-appropriate food or liquid and completely consumed within 1 hour at or below room temperature Reduce dose to once daily in patients with moderate to severe hepatic impairment and those taking concomitant moderate CYP3A inhibitors; reduce dose to twice weekly in patients taking concomitant strong CYP3A inhibitors	Tablets: 150 mg Oral granules in unit-dose packets: 50 mg and 75 mg
lumacaftor/ ivacaftor (Orkambi)	Adults and pediatrics ≥ 12 years of age: two 200/125 mg tablets orally every 12 hours (800/500 mg/day); All doses should be administered with fat-containing food Reduce dose in patients with moderate or severe hepatic impairment (throughout treatment) and when initiating lumacaftor/ivacaftor in patients already taking strong CYP3A inhibitors (first week only)	Tablets: 200/125 mg

* The Special Populations and Drug Interactions sections offer additional dosing details.

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Study Measure(s)

Cystic Fibrosis Questionnaire-Revised (CFQ-R): The CFQ-R measures the overall health, daily life, perceived well-being, and symptoms in patients with CF and may be self-administered, proxy-administered, or done via an interview for children.[37] Three versions are available: one for persons ≥ 14 years old and two for children ages 6 to 13 years (one for parents and one for the child). Each version varies slightly in item numbers (range 35 to 50), but all have 9 quality of life domains (physical,

role/school, vitality, emotion, social, body image, eating, treatment burden, health perceptions) and 3 symptom scales (respiratory, digestive, and weight). Each component is scored on a 4-point Likert scale with a total score ranging from 0 to 100 (higher scores indicating better health).

ivacaftor (Kalydeco) versus placebo in patients with a *G551D CFTR* mutation

STRIVE: The safety and efficacy of ivacaftor for the treatment of CF patients with a *G551D CFTR* mutation was evaluated in a randomized, double-blind, placebo-controlled clinical trial in 161 patients.[38,39] Patients ≥ 12 years old (mean, 25.5 years) with CF and a FEV_1 of 40% to 90% (mean, 63.6%) the predicted value were randomized 1:1 to either 150 mg oral ivacaftor or placebo every 12 hours with fat containing food for 48 weeks in addition to their currently prescribed CF therapies (e.g., tobramycin, dornase alfa). Use of hypertonic saline was not allowed, and those with persistent abnormal liver function or with *Burkholderia cenocepacia*, *Burkholderia dolosal*, or *Mycobacterium abscessus* in their sputum were excluded. The treatment difference between ivacaftor and placebo in mean change in FEV_1 from baseline to week 24, the primary endpoint, was 10.6% ($p<0.0001$, favoring ivacaftor), and these changes persisted through the 48 weeks. No key differences were found in subgroups. Significant differences were also found between ivacaftor and placebo at Weeks 24 and 48 in mean change from baseline in Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain score, mean absolute change from baseline in body weight, and absolute change in sweat chloride ($p\leq0.001$ for all measures). Ivacaftor also reduced the risk of pulmonary exacerbation compared to placebo at Week 48 (hazard ratio [HR], 0.455; $p=0.001$). Adverse effects were similar between the two groups.

ENVISION: A nearly identically designed trial assessed the safety and efficacy of ivacaftor for the treatment of CF patients with a *G551D CFTR* mutation was evaluated in a randomized, double-blind, placebo-controlled clinical trial in 52 patients.[40,41] Patients 6 to 11 years old (mean, 8.9 years) with CF and a FEV_1 of 40% to 105% (mean, 84.2%) the predicted value were randomized 1:1 to either 150 mg oral ivacaftor or placebo every 12 hours with fat containing food for 48 weeks in addition to their currently prescribed CF therapies. Like the former trial, use of hypertonic saline was not allowed, and those with persistent abnormal liver function or with *B. cenocepacia*, *B. dolosal*, or *M. abscessus* in their sputum were excluded. The treatment difference between ivacaftor and placebo in mean change in FEV_1 from baseline to week 24, the primary endpoint, was 12.5% ($p<0.0001$, favoring ivacaftor), and these changes persisted through the 48 weeks (mean change in FEV_1, 10%; $p<0.001$). No key differences were found in subgroups. Significant differences were also found between ivacaftor and placebo at Weeks 24 and 48 mean absolute change from baseline in body weight and absolute change in sweat chloride ($p<0.001$ for all measures). No significant differences were found between ivacaftor and placebo at Weeks 24 and 48 in mean change from baseline in CFQ-R respiratory domain score. Adverse effects were similar between the two groups.

ivacaftor (Kalydeco) versus placebo in patients with a *G1244E*, *G1349D*, *G178R*, *G551S*, *G970R*, *S1251N*, *S1255P*, *S549N*, or *S549R CFTR* mutation

KONNECTION: A 2-part, randomized, double-blind, placebo-controlled crossover trial assessed the efficacy and safety of ivacaftor in CF patients ≥ 6 years old (mean, 23 years) with a *G1244E*, *G1349D*, *G178R*, *G551S*, *G970R*, *S1251N*, *S1255P*, *S549N*, or *S549R CFTR* mutation (n=39).[42,43] Patients with a FEV_1 ≥ 40% at screening (mean, 78%) were randomized 1:1 to ivacaftor 150 mg orally every 12 hours with fat-containing food or placebo for 8 weeks in addition to their currently prescribed CF therapies.

Patients then received the opposite therapy for a second 8 weeks following a 4- to 8-week washout period. A 16-week open label extension trial followed (part 2). Use of inhaled hypertonic saline was not allowed, and those with abnormal liver function or with *B. cenocepacia*, *B. dolosal*, or *M. abscessus* in their sputum were excluded. The model adjusted absolute mean treatment difference between ivacaftor and placebo in FEV_1 from baseline to Week 8, the primary endpoint, was 10.7% (95% CI, 7.3 to 14.1, favoring ivacaftor; p<0.0001). Other efficacy endpoints at Week 8 also demonstrated superiority of ivacaftor over placebo (mean change in BMI = 0.66 kg/m^2 [p<0.0001]; CFQ-R respiratory domain score = 9.6 [p=0.0004]; change in sweat chloride = -49.2 mmol/L [p<0.0001]). Efficacy varied among the different mutations and was not established in patients with a *G970R CFTR* mutation; ivacaftor is not approved in patients with this mutation.

ivacaftor (Kalydeco) versus placebo in patients with a *R117H CFTR* mutation

KONDUCT: The safety and efficacy of ivacaftor for the treatment of CF patients with a *R117H CFTR* mutation was evaluated in a phase 3, randomized, double-blind, placebo-controlled clinical trial in 69 patients.[44,45] Patients ≥ 6 years old (mean, 31 years) with CF and a FEV_1 of 40% to 90% the predicted value in those ≥ 12 years old or a FEV_1 of 40% to 105% the predicted value in those 6 to 11 years old (mean, 73%) were randomized 1:1 to either 150 mg oral ivacaftor or placebo every 12 hours with fat containing food for 24 weeks in addition to their currently prescribed CF therapies. Patients with persistent abnormal liver function or with *B. cenocepacia*, *B. dolosal*, or *M. abscessus* in their sputum were excluded. The treatment difference between ivacaftor and placebo in mean change in FEV_1 from baseline to week 24, the primary endpoint, was 2.1% (p=not significant [NS]). Statistically significant differences were found between ivacaftor and placebo at Week 24 in mean change from baseline in CFQ-R respiratory domain score (mean difference, 8.4; 95% CI, 2.2 to 14.6) and absolute change in sweat chloride (mean difference, -24 mmol/L; 95% CI, -28 to -19.9). No significant difference was found in change in BMI (0.3 kg/m^2; p=NS) or time to first pulmonary exacerbation (hazard ratio [HR], 0.93; p=NS).

lumacaftor/ivacaftor (Orkambi) versus placebo in patients homozygous for the *F508del CFTR* mutation

TRAFFIC and TRANSPORT are two phase 3, multinational, randomized, double-blind, placebo-controlled, parallel-group studies nearly identical in design that compared the safety and efficacy of lumacaftor/ivacaftor to placebo.[46] Stable CF patients 12 years or older who were homozygous for the *F508del CFTR* mutation and with a FEV_1 40% to 90% of the predicted normal value (mean 61%) were randomized to receive lumacaftor (600 mg once daily or 400 mg every 12 hours) in combination with ivacaftor (250 mg every 12 hours) or placebo every 12 hours for 24 weeks. A total of 1,108 patients underwent randomization (1:1:1) and received study drug from both trials. The primary endpoint of both studies was absolute change from baseline in the percentage of predicted FEV_1 at week 24. Secondary endpoints included relative change from baseline in the percentage of predicted FEV_1, absolute change from baseline in body-mass index (BMI), absolute change from baseline in the patient-reported CFQ-R respiratory domain score, percentage of patients with a relative increase from baseline of 5% or higher in the percentage of predicted FEV_1, number of pulmonary exacerbations, time to the first pulmonary exacerbation, and absolute change in body weight. The key differences between the two studies were that TRAFFIC (n=559) included ambulatory electrocardiography while TRANSPORT (n=563) included adolescent pharmacokinetic assessments.

In both studies, there were significant improvements in the primary endpoint in both lumacaftor/ivacaftor dose groups at 24 weeks; the difference between active treatment and placebo with respect to the mean absolute improvement in the percentage of predicted FEV_1 ranged from 2.6 to 4 percentage points ($p<0.001$ for both comparisons), which corresponded to a mean relative treatment difference of 4.3 to 6.7% ($p<0.001$ for both). The percentage of patients who had a relative improvement in the percentage of predicted FEV_1 of 5% or higher was greater in the lumacaftor/ivacaftor groups than in the placebo group ($p<0.001$ to $p=0.002$ for the odds ratio), but was also not significant in the testing hierarchy. In a pooled analysis of both dosing groups, a higher number of patients taking lumacaftor/ivacaftor had a relative improvement in the percentage of predicted FEV_1 of 5% or higher (39% to 46% versus 22%, respectively) and 10% or higher (24% to 27% versus 13%, respectively) compared to placebo. In a pre-planned analysis, FEV_1 was consistent across subgroups (e.g., age, gender, baseline FEV_1, *Pseudomonas aeruginosa* infection status). Clinically meaningful reductions in the rates of protocol-defined pulmonary exacerbations were seen in both lumacaftor/ivacaftor dose groups (rate ratio versus placebo, 0.57 to 0.72; $p<0.001$ to $p=0.05$). However, none of the rate ratios were considered significant in the testing hierarchy. The rates of exacerbations were also lower with both lumacaftor/ivacaftor doses compared to placebo in the pooled analysis (30% to 39% relative reductions; $p=0.001$ and $p<0.001$). In terms of CFQ-R respiratory domain score, there were improvements in the within-group scores, but the treatment difference versus placebo was of limited significance in the pooled analysis. The absolute change in BMI of lumacaftor/ivacaftor versus placebo was 0.36 to 0.41 kg in TRANSPORT ($p<0.001$ for both doses) and 0.13 to 0.16 kg in TRAFFIC (p=NS for both doses). The incidences of adverse events were generally similar in the lumacaftor/ivacaftor and placebo groups. The rate of discontinuation due to an adverse event was 4.2% among patients who received lumacaftor/ivacaftor versus 1.6% among those who received placebo.

SUMMARY

Pulmonary disease is the leading cause of morbidity and mortality in patients with cystic fibrosis (CF). Ivacaftor (Kalydeco) and lumacaftor/ivacaftor (Orkambi) are the newest oral agents, cystic fibrosis transmembrane conductance regulator (*CFTR*) potentiators, FDA-approved to treat CF. Each is approved for a specific subset of CF patients with certain mutations of the *CFTR* protein. Ivacaftor is approved for *R117H*, *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, or *S549R* mutations in patients ≥ 2 years of age while lumacaftor/ivacaftor is indicated in patients ≥ 12 years of age who are homozygous for the *F508del* mutation.

Both Ivacaftor (Kalydeco) and lumacaftor/ivacaftor (Orkambi) carry warnings for elevated transaminases, lens opacities, and significant drug interactions. Other warnings associated with lumacaftor/ivacaftor (Orkambi) include worsening liver function respiratory events. Both ivacaftor and lumacaftor/ivacaftor are dosed twice daily with fat-containing food. Each is available as a tablet and ivacaftor is also available as oral granules for mixing with age-appropriate food.

Each agent has demonstrated efficacy compared to placebo in phase 3 clinical trials which also allowed use of other agents for the symptomatic treatment of CF. Lumacaftor/ivacaftor has shown only modest improvements in pulmonary function and in reducing the risk of pulmonary exacerbations. These agents are approved for differing populations and have not been compared in head-to-head clinical trials. Long-term clinical trials are needed to explore whether or not the use of *CFTR* potentiators will

reduce the use of other agents for the symptomatic treatment of CF (e.g., inhaled antibiotics, dornase alfa [Pulmozyme]) or have a significant mortality benefit.

Current clinical guidelines from the Cystic Fibrosis Foundation (CFF) and Clinical Pharmacogenetics Implementation Consortium (CPIC) have addressed and recommend the use of ivacaftor (Kalydeco) in patients ≥ 6 years of age with at least one *G551D CFTR* mutation; however, both were published prior to the approval of expanded indications for ivacaftor (e.g., patients ≥ 2 years of age, other mutations). Likewise, these were published prior to the approval of lumacaftor/ivacaftor. The guidelines recommended ivacaftor in addition to other CF treatments; ivacaftor was not recommended to replace other treatments for CF.

CFTR potentiators offer an additional treatment option for the treatment of CF in patients with corresponding mutations in the *CFTR* gene, offering a method of improving the disease pathogenesis rather than disease symptom management.

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